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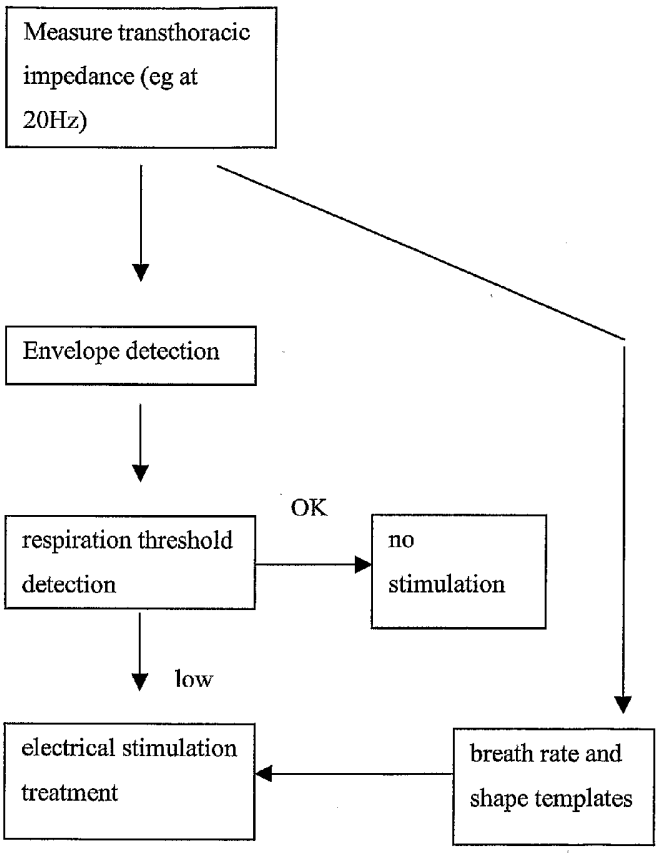
(54) Title: METHOD AND APPARATUS FOR DETECTION AND TREATMENT OF RESPIRATORY DISORDER BY IMPLANTABLE DEVICE



(57) Abstract: Methods and apparatus for detection and treatment of respiratory disorders using implanted devices are described. In one form, afferent nerves are electrically or electro-mechanically stimulated to increase the tone of upper airway muscles. Detection of respiratory disorders is carried out using electrodes implanted in sub-pectoral regions. Open and closed airway apneas are distinguished using a combination of acoustic detectors and electrical transducers.

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GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHOD AND APPARATUS FOR DETECTION AND TREATMENT OF RESPIRATORY DISORDER BY IMPLANTABLE DEVICE

The present application claims priority to US Provisional patent application 60/546,551 filed 20 February 2004.

1.0 FIELD OF THE INVENTION

The invention relates to the detection and treatment of respiratory disorders by implantable electrical and/or electro-mechanical devices.

2.0 BACKGROUND

Nasal CPAP treatment of Sleep Disordered Breathing (SDB), for example as taught by Sullivan in US Patent 4,944,310 has become the standard. However, other techniques are known. Uvulopalatopharyngoplasty (UPPP) is a surgical procedure for the treatment of severe Obstructive Sleep Apnea (OSA). In UPPP, soft tissue on the back of the throat and soft palate (the uvula) is removed. Oral Mandibular Advancement Devices are dental appliances used to treat patients with Obstructive Sleep Apnea (OSA) and Upper Airway Resistance Syndrome (UARS). They look similar to mouth guards used in sports. Other techniques involve electrical stimulation.

US Patent 6,636,767 describes how an electrode is placed in stimulating contact with an airway passage-controlling muscle of the patient. The electrode is energized to contract the muscle and alter the airway passage.

However some researchers have noted (Guilleminault et al. Chest 1995 **107**:67-73) that "The results obtained by us and others do not, at this time, give convincing support for the use of electrical stimulation using submental surface or intraoral electrodes as a viable approach for effective control of obstructive sleep apnea syndrome symptoms."

It is known that central apnea and obstructive apnea can be discriminated by flow and effort sensors. See for example US Patents 6,675,797; 6,029,665; and 6,445,942.

It is an object of the invention to provide improved detection and treatment of respiratory disorders using implanted devices.

3.0 SUMMARY OF THE INVENTION

In accordance with a first aspect of the invention, treatment of a respiratory disorder utilises afferent nerve stimulation.

In accordance with a second aspect of the invention, treatment of a respiratory disorder utilises efferent nerve stimulation.

In accordance with another aspect of the invention, upper airway muscle tone is indirectly stimulated.

In accordance with another aspect of the invention, baseline treatment is initiated when the patient is asleep in order to achieve an increased background tone of upper airway muscles to prevent airway collapse.

In accordance with another aspect of the invention, treatment is initiated or increased above baseline treatment when obstructive sleep apnea is detected.

In accordance with another aspect of the invention, respiratory disorders are detected with the use of an implanted device.

In accordance with another aspect of the invention, open and closed airway (also called, central and obstructive) apneic events are distinguished by a combination of implanted electrodes and acoustic transducers.

4.0 BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 shows method for detection and treatment of respiratory disorders using implantable devices.

5.0 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

5.1 Treatment

For treatment of detected Obstructive Sleep Apnea (OSA), one method is electrical stimulation of afferent nerves, the objective of which is to indirectly cause an increase of the tone of upper airway muscles normally involved with maintenance of upper airway patency. In OSA, it is known that tone of these upper airway muscles typically decreases, contributing to a collapse and obstruction of the airway. Typically during wakefulness in patients with OSA, reflexes work to maintain tone in upper airway muscles thereby preventing airway collapse. The object of the present method is to substitute or enhance this reflex mechanism during sleep, thereby restoring or maintaining airway patency. The site of electrical stimulation is within or adjacent to the genioglossus muscle or in the vicinity of the hypoglossal motor nucleus or excitatory afferent nerve pathways leading to this structure. The amplitude, frequency and pulse width of electrical stimulation is controlled such that sufficient stimulation of afferent nerves is achieved without significant stimulation of efferent nerves, and without eliciting arousal from sleep. This stimulation of afferent nerves thus influences the patient's own intrinsic control system which modulates upper airway tone. The electrical simulation of afferent nerves typically consists of trains of electrical pulses, for example; 0.1 mA amplitude, 0.1 ms duration, train length of 10-30 pulses repeated every 1 minute. This level is defined as 1 unit of stimulation.

A second method for stimulation of afferent nerves is by using mechanical stimulation. A mechanical element, for example a piezo-electric element, is implanted at a site in the vicinity of the upper airway, for example, within or adjacent to the base of the genioglossus muscle. The element is electrically connected to the controller of the implanted device. The controller elicits vibration of the mechanical element by sending an electrical signal. Vibration of the element elicits stimulation of mechanoreceptor

afferent nerve endings within the upper airway. Stimulation of these mechanoreceptors provides an excitatory input into the patient's intrinsic control system of the upper airway, thereby increasing tone of upper airway muscles and hence restoring or maintaining airway patency. The amplitude, frequency and duration of the mechanical stimulation are controlled such that sufficient stimulation of afferent nerves is achieved without sensory stimulation sufficient to cause arousal from sleep. The mechanical simulation of afferent nerves would typically be achieved by a period of several seconds of vibration at frequencies in the range of 10-50 Hz, and is tuned to the frequency at which the target receptors are most sensitive. The repetition rate of the stimulation is controlled according to the detected state of the airway.

For either electrical or mechanical stimulation, the level of stimulation depends on 2 factors: 1) sleep state; 2) state of upper airway. When the patient is awake, no treatment is delivered. When the patient is asleep, a baseline treatment is delivered which has the objective of increasing the background tone of the upper airway muscles such that it is similar to the tone during the awake state. This is designed to pre-emptively reduce the incidence of airway collapse. When the patient is asleep and airway obstruction is detected, treatment above the level of the baseline treatment is delivered which has the objective of restoring airway patency. Sleep state is determined by a combination of time of day and postural state, for example when the patient is supine and the time of day is coincident with the patient's normal sleeping time, sleep state is determined as asleep. Time of day is determined by a real time clock within the implanted device and postural state by a position sensor, also contained within the implanted device. When the sleep state is asleep, the baseline level of treatment is initiated. When the sleep state is asleep and obstruction is detected, the level of treatment is increased and maintained until such time as airway obstruction is no longer detected, as follows:

Sleep State/ Airway State	awake	asleep	Asleep plus airway obstruction

Treatment level	No treatment	Baseline treatment of 0-5 units	Incremental above baseline of 1-10 units

An example of a methodology as described is illustrated in Figure 1.

5.2 Detection of respiratory disorders via implanted electrodes

5.2.1 Impedance

Implanted electrodes are ideally placed one either side of the thoracic cavity. eg one electrode is placed in the left sub pectoral region and a second electrode in the right sub pectoral region. One of these electrodes could be incorporated into the metallic case of an implanted device.

The transthoracic impedance is measured by emitting high frequency (eg 20Hz) electrical pulses (compared with respiration or heart rate) that have amplitude and duration below the level needed to stimulate excitable tissue.

Typically current pulses of 1 mA amplitude and 15 micro second duration are emitted at a 20 Hz. This level of energy is well below the level required to stimulate excitable tissue.

The impedance changes are calculated by measuring current & voltage and calculating impedance via Ohm's Law. Impedance changes are correlated with thorax movements. Patterns of movement are detected and used to indicate a variety of respiratory disorders such as Obstructive Apnea, central apnea, Cheyne-Stokes respiration (CS-R).

To detect impedance changes the instantaneous transthoracic impedance signal is compared to a baseline reference. eg the baseline reference is a continuously updated average of the most recent 30 minutes of the transthoracic impedance signal.

The changes the transthoracic impedance signal are analysed in order to determine the state of respiration as follows:

Respiration type	Transthoracic impedance
Normal respiration – no SDB	rhythmic variations at a rate of between 6 and 25 per minute; this rate averaged over; eg 2 minutes.Similarily an amplitude reference for 'normal breathing' is also derived; eg average amplitude of rhythmic variations over 30 minutes.
Obstructive	Marked reduction of amplitude as compared to the above reference; eg reduction of 30% or more; for at least 10 seconds.
Central apnea	first derivative of the impedance signal = essentially zero; no rhythmic variations for a period of 10 seconds or more
CSR	Derive the envelope of the rhythmic variations. Crescendo-decrescendo pattern denoted by a rhythmic variation in the envelope with a period of typically between 40 and 120 seconds or other classifier system.

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5.2.2 Impedance and acoustic transducers

A method for measuring airflow in an implantable device is by use of an acoustic transducer inside the device, such as a microphone, or from a transmitted signal from an
10 external device in communication with the implantable device. Analysis of the frequency and amplitude of the sound can be used to deduce relative airflow. In addition, snoring,

which is indicative of a partial obstruction of the upper airway can be detected. It is known that snoring is frequently a precursor of obstructive apnea.

A method for indicating thoracic movement is by measuring the electrical impedance between two or more implanted electrodes.

By a combination of methods for deducing airflow and thoracic movement, it is possible to discriminate between central and obstructive apnea in an implantable device. For example, if thoracic movements are detected without corresponding airflow, it is possible to deduce that there is obstructive apnea occurring. If there is no airflow and no thoracic movements for a specified period, it is possible to deduce that there is central apnea.

CLAIMS

1. A method of treating sleep disordered breathing comprising the step of electrical stimulation of nerves to increase muscle tone of upper airway muscles.

2. A method as claimed in claim 1 whereby the afferent nerves are stimulated.

3. The method of claim 2 whereby the site of electrical stimulation is within or adjacent to the genioglossus muscle.

4. The method of claim 2 whereby the site of electrical stimulation is in the vicinity of the hypoglossal motor nucleus or excitatory afferent nerve pathways leading to this structure.

5. The method of claim 1 whereby the electrical stimulation comprises trains of electrical pulses.

6. The method of claim 5 whereby the train length is approximately 10-30 pulses.

7. A method of treating sleep disordered breathing comprising the step of mechanical stimulation of nerves to increase muscle tone of upper airway muscles.

8. The method of claim 7 whereby mechanical stimulation is performed by a piezo electric mechanical element implanted at a site in the vicinity of the upper airway.

9. The method of claim 8 whereby the piezo-electric mechanical element is implanted within or adjacent to the base of the genioglossus muscle.

10. The method of claim 7 whereby the mechanical stimulation is periodic.

11. The method of claim 10 whereby the period is in the order of several seconds of vibration.

12. The method of claim 7 whereby the mechanical vibration occurs at frequencies in the range of 10-50 Hz.

13. The method of claim 1 or 7 whereby stimulation is repeated in accordance with the detected state of the airway.

14. The method of claim 1 or 7 whereby stimulation is carried out in accordance with a model of Cheyne-Stokes Respiration.

15. Apparatus for treating respiratory disorders comprising a piezo-electric mechanical element, adapted for implant within or adjacent the base of genioglossus muscle and a controller, adapted to elicit vibration of the element via an electrical signal.

16. A method of detecting respiratory disorders comprising the step of measuring a transthoracic impedance changes via implanted electrodes.

17. The method of claim 16 whereby a first electrode is placed in the left sub-pectoral region.

18. The method of claim 16 whereby a second electrode is placed in the right sub-pectoral region.

19. The method of claim 16 whereby the transthoracic impedance is measured by emitting high frequency electrical pulses.

20. The method of claim 19 whereby the frequency of the pulses is high compared to typical respiration or heart rate.

21. The method of claim 19 whereby the frequency of the pulses is approximately 20 Hz.

22. The method of claim 19 whereby the pulses are of approximately 1mA amplitude.

23. The method of claim 19 whereby the pulses are of approximately 15 microsecond duration.

24. The method of claim 19 whereby an impedance signal is compared to a baseline reference.

25. The method of claim 24 whereby the baseline reference is continuously updated.

26. The method of claim 24 whereby the signal having rhythmic variations at a rate of between approximately 6 and 25 per minute is taken as being indicative of normal respiration.

27. The method of claim 24 whereby the signal having a marked reduction in amplitude compared to the reference is taken as being indicative of an obstructive apnea.

28. The method of claim 24 whereby the signal having a first derivative of near zero is taken as being indicative of central apnea.

29. The method of claim 24 whereby the signal having a crescendo-decrescendo pattern with a period of approximately 40 to 120 seconds is taken as being indicative of Cheyne-Stokes Respiration.

30. A method of distinguishing open and closed airway apneic events are distinguished by a combination of implanted electrodes and acoustic transducers.

31. A method of treating respiratory disorders as shown and illustrated in Fig. 1

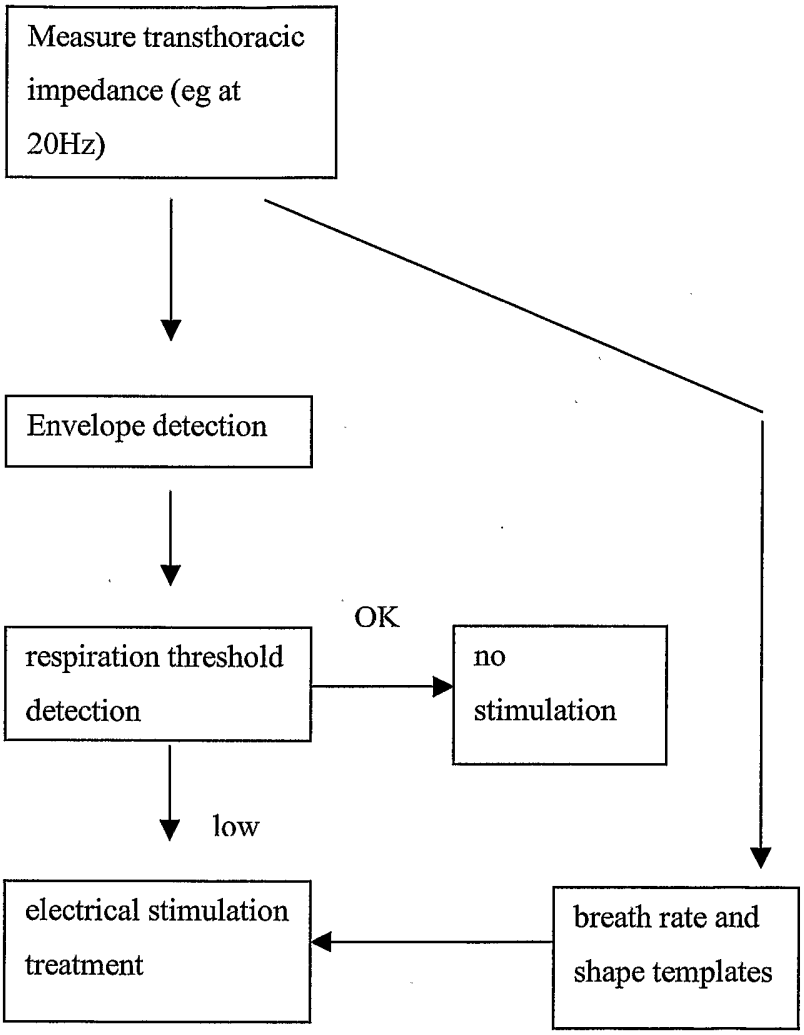
Measure transthoracic impedance (eg at 20Hz)
Envelope detection
respiration threshold detection
OK
no stimulation
low
electrical stimulation treatment
breath rate and shape templates

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000225

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61N 1/00, A61M 16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATABASES CONSULTED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI: osa, sleep, breathing, disorder, apnea, hypop, obstruct, airway, cheyne-stokes, electric,electrode, potential, fes, fns, mens, stimulate, nerve, neural, muscle, hypoglossus, genioglossus, pulse.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4830008 A (MEER) 16 May 1989 Abstract, Fig. 1-6, column 5 line 36 – column 6 line 59.	1-6
X	US 5540733 A (TESTERMAN et al.) 30 July 1996 Abstract, Fig. 33,34, column 2 line 43 – column 3 line 31, column 13 line 11 – column 16 line 22	1-6
X	WO 1992015364 A1 (MEER) 17 September 1992 Abstract, Fig. 1-11, page 15 line 20 – page 16 line 23.	1-6
X	EP 0507580 B1 (MEDTRONIC, INC) 31 July 1996 Fig.1-5, column 2 line 50 – column 3 line 28	1-6

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2005	13 APR 2005
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**MATTHEW FORWARD** Telephone No : (02) 6283 2606

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000225

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0702977 B1 (MEDTRONIC, INC) 19 March 2003 Paragraphs [0001], [0004]-[0010], [0024]	1-6
X	WO 1992021407 A1 (MEDTRONIC, INC) 10 December 1992 Abstract, Fig. 1-6, page 5 line 2 – page 6 line 20.	1-6
X	US 6251126 B1 (OTTENHOFF et al.) 26 June 2001 Abstract, Fig. 1-6, column 2 line 35 – column 5 line 63.	1-6
X	US 6240316 A (RICHMOND et al.) 29 May 2001 Abstract, Fig.1-8, column 7 line 52 – column 8 line 43.	1-6

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:1-6

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: III

The claims do not relate to one invention only (or to a group of inventions so linked as to form a single general inventive concept). In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to be "special technical features". These are features that potentially distinguish the claimed combination of features from the prior art. Where different claims have different special technical features they define different inventions. I have found claims having different special technical features as follows:

(1) Claims 1-6. It is considered that –electrical stimulation of nerves to increase muscle tone of upper airway muscles - comprises a first special technical feature.

(2) Claims 7-15. It is considered that – mechanical stimulation of nerves to increase muscle tone of upper airway muscles - comprises a second special technical feature.

(3) Claims 16-29. It is considered that – measuring a transthoratic impedance changes via implanted electrodes - comprises a third special technical feature.

(4) Claim 30. It is considered that – combination of implanted electrodes and acoustic transducers - comprises a fourth special technical feature.

Since these groups of claims do not share any of the special technical features identified, a technical relationship between the inventions does not exist. Accordingly the claims do not relate to one invention or to a single inventive concept, a priori.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2005/000225

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	4830008	NONE					
US	5540733	NONE					
WO	9215364	AU	15302/92	CA	2105075	EP	0576528
		US	5190053				
EP	0507580	US	5215082				
EP	0702977	JP	8224318	US	5540732		
WO	9221407	AU	18988/92	CA	2084312	EP	0541763
		US	5174287				
US	6251126	US	6269269				
US	6240316	US	6345202	US	2001010010		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX